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STERNE KESSLER GOLDSTEIN & FOX
1100 NEW YORK AVENUE NW
SUITE 600
WASHINGTON, DC 200053934

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BUNNER, BRIDGET E	

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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Paper No. 03122004

Application Number: 09/380,704
Filing Date: June 06, 2000
Appellant(s): BUSH ET AL.

Frank R. Cottingham
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 17 December 2003 (hereinafter, the Brief).

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The brief does not contain a statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief. Therefore, it is presumed that there are none. The Board, however, may exercise its discretion to require an explicit statement as to the existence of any related appeals and interferences.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is incorrect.

The amendment after final rejection filed on 17 October 2003 has been entered.

(5) Summary of Invention

The summary of invention contained in the brief is correct. The Examiner respectfully disagrees with Appellant's conclusion that bathocuprione would be effective in treating amyloidosis for reasons of record and re-stated herein.

(6) Issues

The appellant's statement of the issues in the brief is correct.

*(7) **Grouping of Claims***

Appellant's brief includes an accurate statement that the rejected claims do stand or fall together.

*(8) **Claims Appealed***

The copy of the appealed claims contained in the Appendix to the brief is correct.

*(9) **Prior Art of Record***

Cherny et al. Treatment with a copper-zinc chelator markedly and rapidly inhibits beta-amyloid accumulation in Alzheimer's disease transgenic mice. Neuron 30(3):665-676, 2001.

Crapper-McLachlan et al. Intramuscular desferrioxamine in patients with Alzheimer's disease. Lancet 337(8753): 1304-1308, 1991.

Cuajungco et al. Metal chelation as a potential therapy for Alzheimer's disease. Annals NY Acad Sci 920: 292-304, 2000.

Fonte et al. The severity of cortical Alzheimer's type changes is positively correlated with increased amyloid-beta Levels: Resolubilization of amyloid-beta with transition metal ion chelators. J Alzheimers Dis. 3(2):209-219, 2001.

Gillmore et al. Amyloidosis: a review of recent diagnostic and therapeutic developments. Br J Haematol 99(2):245-56, 1997.

Gnjec et al. Transition metal chelator therapy--a potential treatment for Alzheimer's disease? Front Biosci. 7:d1016-23, 2002.

Halliday et al. Alzeimer's disease and inflammation: a review of cellular and therapeutic mechanisms. Clin Exp Pharmacol Physiol 27: 1-8, 2000.

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

35 USC § 112, first paragraph

Claims 1-2 and 37 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The basis for this rejection is set forth in the previous Office Actions (pg 4-6 of the Action of 26 August 2002; pg 4-11 of the Action of 22 May 2003) but is reiterated below in full.

Claim 1 is directed to a method of treating amyloidosis in a subject comprising administering to said subject an effective amount of (a) bathocuproine or a hydrophobic derivative thereof; and (b) one or more pharmaceutically acceptable carriers or diluents; for a time and under conditions to bring about said treatment; and wherein said bathocuprione or hydrophobic derivative thereof reduces, inhibits or otherwise interferes with amyloid beta peptide (Aβ)-mediated production of radical oxygen species. Claim 2 recites further administering to the subject an effective amount of indomethacin. Claim 37 is directed to a pharmaceutical composition comprising (a) bathocuproine or a hydrophobic derivative thereof; and (b) indomethacin or a hydrophobic derivative thereof; and (c) one or more pharmaceutically acceptable carriers or diluents.

The specification teaches that brain tissue is homogenized in water and the specific anti-Aβ monoclonal antibodies are used to assay Aβ extraction by western blot (pg 91, lines 26-28; pg 92, lines 1-2). The specification also teaches that extraction of the same material is repeated with PBS in the presence of chelaters of varying specificities and refers to Table 1. The

specification determines that the presence of a chelator increased the amount of Aβ in the soluble extract (pg 92, lines 3-6; Figure 19). Examination of the total amount of protein released by the treatments reveals that the chelation is not merely liberating more proteins in a non-specific manner (pg 92, lines 14-16). The specification discloses that bathocuproine (BC) exhibits a dose-response increase in Aβ extraction from human brain, most likely due to its relatively high specificity for zinc (pg 94, lines 21-25; pg 100, lines 4-7; pg 101, lines 12-14; Figure 25A-25B; Tables 5, 7-8). The specification also teaches that bathocuproine is less effective in extracting Aβ from control tissue than from Alzheimer's disease (AD) tissue (pg 95, lines 29-30; Figure 20A).

However, the specification of the instant application only outlines a prophetic procedure (not a working example) for a method of treating amyloidosis in a subject by administration of bathocuprione and a pharmaceutically acceptable carrier (pg 43-44). This is not adequate guidance, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. The claimed method may not necessarily treat amyloidosis *in vivo*. The skilled artisan must resort to trial and error experimentation to determine the optimal quantity of bathocuprione or bathocuprione/indomethacin to be administered, as well the duration of treatment and route of administration. Such trial and error experimentation is considered undue. There is little guidance in the specification at pg 45-49 regarding *specific* dosages, duration of treatment, or route of administration for bathocuprione or how to overcome obstacles encountered in prior art disclosures of administration of metal chelators or treating amyloidosis, generally. See Gillmore, Fonte, Cuajungco, and Gnjec. Additionally, as was found in Ex parte Hitzeman, 9 USPQ2d 1821 (BPAI 1987), a single embodiment may provide broad

enablement in cases involving predictable factors such as mechanical or electrical elements, but more will be required in cases that involve unpredictable factors such as most chemical reactions and physiological activity. See also In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970); Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 927 F.2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed. Cir.), cert. denied, 502 U.S. 856 (1991). The present invention is unpredictable and complex wherein one skilled in the art may not necessarily treat amyloidosis by administration of bathocuprione and indomethacin to a subject, wherein bathocuprione reduces, inhibits or otherwise interferes with amyloid beta peptide (Aβ)-mediated production of radical oxygen species. One skilled in the art would also not be able to predict the effects of bathocuproine or bathocuprione/indomethacin in a subject since relevant literature reports that (1) the search continues for a treatment that causes the mobilization of amyloid deposits (Gillmore et al. Brit J Haematol 99: 245-256, 1997; pg 249, col 2) and (2) the administration of other metal chelators to subjects causes high toxicity and severe physiological side effects (Fonte et al. J Alzheimer's Disease 3 : 209-219, 2001, Cuajungco et al. Ann NY Acad Sci 290: 292-304, 2000, and Gnjec et al. Frontiers Biosci 7:1016-1023, 2002). Gillmore et al. indicates that few clinical trials have been performed and the approach to treatment of amyloidosis remains somewhat empirical (pg 250, ¶1). Amyloid deposition is associated with a diverse range of disorders that includes Alzheimer's disease, Type II diabetes mellitus, and dialysis arthropathy and the search continues for a treatment that causes the mobilization of amyloid deposits (Gillmore, abstract, pg 249, col 2). Therefore, it is also noted that a broad, reasonable interpretation of the claims encompasses treatment of such amyloidosis diseases and disorders as Alzheimer's disease, which has proven

to be recalcitrant to treatment in the art (see for example, Halliday et al., Clin Exp Pharmacol Physiol 27: 1-8, 2000).

Additionally, the *in vitro* Aβ solubilization results obtained with the metal chelator, bathocuprione, may not necessarily be indicative of the results obtained with bathocuprione *in vivo* for the treatment of amyloidosis by reducing, inhibiting or interfering with amyloid beta peptide (Aβ)-mediated production of radical oxygen species. It is noted that prior to the filing date of the instant application, several transgenic mouse models for amyloidosis and/or Alzheimer's disease had already been developed and were being utilized in laboratories. Relevant literature discloses that the extraction of Aβ from the cortex of AD brains is significantly enhanced in a dose dependent manner by the presence of the metal ion chelator, TPEN (Fonte et al., J Alzheimer's Disease 3: 209-219, 2001; see abstract; pg 210, ¶ 2). However, the unpredictable effects of the administration of TPEN are evidenced when Fonte discloses that TPEN is of limited benefit to patients because it is highly toxic (pg 217, ¶ 1). Fonte also discloses that AβPP transgenic model animals provide a useful means of further evaluating chelators as potential therapeutic agents for Alzheimer's disease (pg 217, first paragraph). Additionally, a previous clinical trial of the chelator, desferrioxamine (DFO), reports that DFO significantly arrested the progression of AD (Cuajungco et al., Annals NY Acad Sci 920: 292-304, 2000; see pg 299, ¶ 4). However, the unpredictability of the effects of administration of DFO is evidenced since DFO is a charged molecule that does not easily penetrate the blood-brain barrier and is easily degraded after administration (Cuajungco et al., pg 299 ¶ 4). Cuajungco also discloses that the administration of DFO is associated with

discouraging difficulties including the nonspecific problems of systemic metal ion depletion and the problem of administration of a twice-daily, painful intramuscular injection (pg 299, ¶ 4).

Additionally, there are several important points that must be taken into consideration before and during the administration of a metal chelator to a subject, which the instant specification has not addressed with bathocuprione. For example, Gnjec (Frontiers Biosci 7 : 1016-1023, 2002) teaches that if the levels of certain metals are decreased excessively below recommended levels, severe physiological side effects may result (under Part IV, important considerations in chelator therapy). Gnjec also indicates that the depletion of metals should be localized to the site of pathology without a systemic depletion of metal ion concentrations. Gnjec discusses that a prerequisite for successful treatment with any chelator will be the requirement for low toxicity and minimum side effects of the drug itself. Gnjec also adds that a successful treatment strategy may involve a combination of several approaches for both the solubilization and inhibition of redox properties of Aβ in AD brain tissue (last ¶ under part IV).

Furthermore, the specification does not teach how to use a bathocuproine or bathocuprione/indomethacin "pharmaceutical" composition without undue experimentation for the treatment of a disease in an animal. Additionally, the phrase "pharmaceutically acceptable carrier or diluent" in claims 1-2 and 37 recites an intended use of bathocuproine or bathocuproine/indomethacin for treatment or administration in an animal. The specification does not teach how to use bathocuproine or bathocuproine/indomethacin without undue experimentation for the treatment of a disease in an animal.

Due to the large quantity of experimentation necessary to determine the quantity of bathocuproine or bathocuproine/indomethacin to be administered, the most effective

administration route, and the duration of the treatment, the lack of direction/guidance presented in the specification regarding the same, the absence of working examples directed to the same, the complex nature of the invention, and the unpredictability of the effects of the composition *in vivo* (see Fonte et al., Cuajungco et al., Gnjec et al., and Gillmore et al.), undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

(11) Response to Argument

It is noted that at pages 5-7 of the Brief, Appellant cites pertinent case law reviewing the legal standard of enablement. The Examiner takes no issue with Appellant's general comments regarding the legal standard for enablement.

(1) Ability of a skilled artisan to formulate and administer compositions to a subject

Appellant argues at pg 8 and at the top of pg 11 of the Brief that the Examiner has not put forth any evidence to support the assertions that determining (a) the optimal quantity of bathocuprione to be administered, (b) the duration of treatment, and/or (c) the route of administration would have required "trial and error" experimentation. Appellant states that at the time of the filing of the instant application, such parameters were routinely determined and optimized. Appellant indicates that the need for experimentation by itself is not sufficient to support a finding of non-enablement as long as the amount of experimentation is not considered undue and cites *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983, aff'd sub nom., Massachusetts Institute of Technology v. A.B.

Fortia, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985); *In re Wands* 858 F.2d at 737, 8 USPQ2d at 1404. Appellant asserts that the Examiner has not explained why making and using pharmaceutical compositions comprising bathocuprione would have involved a greater amount of experimentation with respect to the determination of quantity, duration, and routes of administration than is required for other compounds, including metal chelators, that have been routinely developed and administered effectively as pharmaceutical compositions in the art. At pg 8 and at the bottom of pg 11 through the top of pg 12 of the Brief, Appellant contends that the specification provides specific guidance as to the amount and timing of administration of chelators such as bathocuprione. Appellant states that the specification describes the relationship between bathocuprione concentration and Aβ solubilization and such information would have instructed a skilled artisan as to the amount and frequency of administration of bathocuprione in order to achieve optimum therapeutic results. In the first full paragraph at pg 12 of the Brief, Appellant argues that a skilled artisan would have also been guided by the knowledge generally available in the art regarding the preparation and administration of pharmaceutical compositions and cites *Genentech, Inc. v. Novo Nordisk*, 108 F.3d 1361, 1366, 42 USPQ2d 1001, 1005 (Fed. Circ. 1997); *Hybritech v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986). At pg 8-9 and 12 of the Brief, Appellant adds that since general methods for formulating and administering pharmaceutical compositions were well known in the art, such information should be regarded as supplementing the teachings in the specification.

Appellant's arguments have been fully considered but are not found to be persuasive. The specification at pg 12-17 and 41-49 only outlines a prophetic procedure (not a working example) for treating amyloidosis in a subject by administering bathocuprione. However, this is

not adequate guidance, but is merely an invitation for the artisan to use the current invention as a starting point for further experimentation. The claimed method may not necessarily treat amyloidosis *in vivo*. For example, the prophetic example does not provide the skilled artisan with detailed guidance for administration of bathocuprione, including the optimal dosage and duration of administration of bathocuprione or bathocuprione/indomethacin. The specification only teaches that "the pharmaceutical forms containing the active agents may be administered in any convenient manner either orally or parenteraly, such as by intravenous, intraperitoneal, subcutaneous, rectal, implant, transdermal, slow release, intrabuccal, intracerebral or intranasal administration. Generally, the active agents need to pass the blood brain barrier and may have to be chemically modified, e.g. made hydrophobic, to facilitate this or be administered directly to the brain or via other suitable routes" (pg 46, lines 8-14). The specification also discloses that "a unit dosage form can, for example, contain the principal active compound in amounts ranging from 0.5 μg to about 2000 mg. Alternatively, amounts ranging from 200 ng/kg/body weight to above 10 mg/kg/body weight may be administered. The amounts may be for individual active agents or for the combined total of active agents" (pg 48, lines 29-30, pg 49, lines 1-3). Such broad brush assertions do not constitute adequate guidance to practice the claimed method, but rather constitute an invitation to experiment empirally to determine how to practice the suggested method to obtain the therapeutic results required by the claims. The specification discloses numerous modes of administration as well as a broad range of dosage amounts. Although Appellant submits that parameters such as dosages and timing and methods of administration of therapeutic agents may need to be optimized and that optimization is routine, there is little guidance in the specification for one skilled in the art to determine these optimal conditions.

Such trial and error experimentation is considered undue. Furthermore, a large quantity of experimentation would be required by the skilled artisan to treat all possible diseases and disorders associated with amyloidosis, such as Alzheimer's disease and Type II diabetes mellitus, which are encompassed by the instant claims.

A specification may be enabling even though some experimentation is necessary, but the amount of experimentation, however, must not be unduly extensive. According to MPEP § 2164.06, "the guidance and ease in carrying out an assay to achieve the claimed objectives may be an issue to be considered in determining the quantity of experimentation needed". Additionally, as was found in Ex parte Hitzeman, 9 USPQ2d 1821 (BPAI 1987), a single embodiment may provide broad enablement in cases involving predictable factors such as mechanical or electrical elements, but more will be required in cases that involve unpredictable factors such as most chemical reactions and physiological activity. See also In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970); Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 927 F.2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed. Cir.), cert. denied, 502 U.S. 856 (1991). The present invention is unpredictable and complex wherein one skilled in the art may not necessarily treat amyloidosis by administration of bathocuprione or bathocuprione/indomethacin to a subject. Evidence supporting this statement has been cited on the record. (See Gillmore, Fonte, Cuajungco, and Gnjec.) Additionally, bathocuprione may not necessarily reduce, inhibit or interfere with amyloid beta peptide (Aβ)-mediated production of radical oxygen species, as required by the claims.

Furthermore, it is noted that the fact patterns of the cases cited by the Appellant (*In re Certain Limited-Charge Cell Culture Microcarriers, Genentech, Inc. v. Novo Nordisk, Hybritech*

v. Monoclonal Antibodies, Inc.) and the fact pattern of the instant rejection are significantly different, and the court decisions are not binding with regard to the instant rejections. For example, in *Certain Limited-Charge Cell Culture Microcarriers,* the main issue was patent validity and unfair competition. The patented claims are drawn to microcarrier beads for cell culture and a method of using the microcarriers for cell culture, not administration of a compound or claims to a pharmaceutical composition. Regarding *Genentech, Inc. v. Novo Nordisk* and *Hybritech v. Monoclonal Antibodies, Inc.*, the Court of Appeals Federal Circuit indicated that the specification does not need to disclose what is already well known in the art. However, if there is no disclosure of any starting material or any conditions under which the claimed process can be carried out, undue experimentation is required and there is a failure to meet the enablement requirement that cannot be rectified by asserting the disclosure related to the process is within the skill of the art. Evidence has been cited on the record establishing that the prior has not disclosed how to overcome significant obstacles encountered when administering metal chelators or treating amyoidosis generally. See Gillmore, Fonte, Cuajungco, and Gnjec.

(2) Does bathocuprione, when administered to a subject, treat amyloidosis?

At pg 9 of the Brief, Appellant argues that a *prima facie* case of non-enablement has not been established. At the bottom of pg 13 of the Brief, Appellant notes that the Examiner's arguments, as a whole, represent an improper attempt to shift the initial burden regarding the enablement of the invention to Appellant. Appellant states that the initial burden in demonstrating that a claimed invention is not enabled lies with the Examiner. Appellant argues

that the Examiner has rejected the claims, not because there is any specific evidence to indicate that the invention does not work, but because, in the Examiner's view, Appellant has not proven that the invention does work. Appellant cites *In re Wright*, 999 F.2d at 1562, 27 USPQ2d at 1513. Contrary to Appellant's assertion, the Examiner has set forth specific evidence and sound scientific reasoning to indicate that making and/or practicing the subject matter encompassed by the claims would have required undue experimentation. The Examiner set forth a reasonable explanation of why the scope of protection provided by the claims is not adequately enabled by the specification's description of the invention (pg 4-6 of the Action of 26 August 2002; pg 4-11 of the Action of 22 May 2003). Specifically, proper analysis of the Wands factors was provided in the previous Office Actions. Due to the large quantity of experimentation necessary to determine the quantity of bathocuproine or bathocuproine/indomethacin to be administered, the most effective administration route, and the duration of the treatment, the lack of direction/guidance presented in the specification regarding the same, the absence of working examples directed to the same, the complex nature of the invention, and the unpredictability of the effects of the composition *in vivo* (see Fonte et al., Cuajungco et al., Gnjec et al., Gillmore et al.), undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope. Since the PTO met the initial burden of setting forth a reasonable explanation of why the claims are not adequately enabled, the burden shifts to Appellant to provide suitable evidence to indicate that the specification is enabling (see *In re Wright).*

Furthermore, the arguments of counsel cannot take the place of evidence in the record. In the instant case the Appellant is asserting that bathocuprione would be effective at treating

amyloidosis and reducing, inhibiting, or interfering with Aβ-mediated production of radical oxygen species when administered to a subject while no data, information, or teaching supports the treatment of amyloidosis by bathocuprione in the instant Specification {see *In re Schulze*, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965); *In re Geisler*, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997) ("An assertion of what seems to follow from common experience is just attorney argument and not the kind of factual evidence that is required to rebut a prima facie case of obviousness.") and MPEP § 716.01(c)}.

(a) Working Example

At pg 14-15 of the Brief, Appellant contends that the absence of a working example is not sufficient to establish a *prima facie* case of non-enablement. Appellant indicates that the specification need not contain a working example if the invention is otherwise disclosed in such a manner that one skilled in the art would have been able to practice it without undue experimentation and cites *Gould v. Quigg*, 822 F.2d 1074, 1078, 2 USPQ2d 1302, 1304 (Fed. Cir. 1987) ; *in re Borkowski*, 422 F.2d 904, 908, 164 USPQ 642, 645 (CCPA 1970). Appellant submits that a person of ordinary skill in the art would have been able to make, use and practice the subject matter encompassed by the claims using routine methods in the art.

Appellant's arguments have been fully considered but are not found to be persuasive. Although Appellant need not to have actually reduced the invention to practice prior to filing the application, the lack of a working example is only one factor to be considered, especially in a case involving an unpredictable art (MPEP § 2164.02). The specification at pg 12-17 and 41-49 only outlines a prophetic procedure (not a working example) for treating amyloidosis in a subject

by administering bathocuprione. However, this is not adequate guidance, but is merely an invitation for the artisan to use the current invention as a starting point for further experimentation. The claimed method may not necessarily treat amyloidosis *in vivo*. Also, bathcuprione may not necessarily reduce, inhibit or interfere with amyloid beta peptide (Aβ)-mediated production of radical oxygen species, as required by the claims. The skilled artisan must resort to trial and error experimentation to determine the optimal quantity of bathocuprione/indomethacin to be administered, as well the duration of treatment and route of administration. Such trial and error experimentation is considered undue. There is little guidance in the specification at pg 12-17 and pg 41-49 regarding specific dosages, duration of treatment, and type of administration for bathocuprione or how to overcome obstacles encountered in prior art disclosures of administration of metal chelators or treating amyloidosis, generally. See Gillmore, Fonte, Cuajungco, and Gnjec. The specification only discloses numerous modes of administration as well as a broad range of dosage amounts. Additionally, as was found in Ex parte Hitzeman, 9 USPQ2d 1821 (BPAI 1987), a single embodiment may provide broad enablement in cases involving predictable factors such as mechanical or electrical elements, but more will be required in cases that involve unpredictable factors such as most chemical reactions and physiological activity. See also In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970); Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 927 F.2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed. Cir.), cert. denied, 502 U.S. 856 (1991). The present invention is unpredictable and complex wherein one skilled in the art may not necessarily treat amyloidosis or reduce, inhibit, or interfere with Aβ-mediated production of radical oxygen species by administration of bathocuprione and indomethacin to a subject. Evidence supporting this statement has been cited

on the record. See Gillmore, Fonte, Cuajungco, and Gnjec. Therefore, the skilled artisan may also not necessarily treat all possible diseases and disorders associated with amyloidosis, such as Alzheimer's disease and Type II diabetes mellitus, which are encompassed by the instant claims.

Additionally, although a specification may lack a working example, the specification must provide sufficient guidance so that one skilled in the art can practice the claimed invention without undue experimentation. At pg 19 of the Brief (3rd full paragraph), Appellant states that the physiological conditions that exist in brain homogenates (e.g. pH, ion concentration, macromolecular content, etc.) closely approximate the conditions found in the brain tissue environment *in vivo*. However, the utilization of brain homogenates in Examples 5-7 of the instant specification (pg 90-121) is not an art-recognized, predictive model system for amyloidosis. One skilled in the art would not be able to predict that the results observed with the brain homogenates (solubilization of Aβ) would be indicative of results found *in vivo* with bathocuprione. It is noted that prior to the filing date of the instant application, several transgenic mouse models for amyloidosis and/or Alzheimer's disease had already been developed and were being utilized in laboratories. It is also not clear to the Examiner how brain homogenates approximate brain tissue *in vivo* since there are many other variables present in brain tissue *in vivo* that are not present in the brain homogenates of the specification, such as specific oxygen levels, carbon dioxide levels, temperature, blood/cell circulation, growth factors, other metals ions, etc.

It is noted that the fact patterns of the cases cited by the Appellant (*Gould v. Quigg* and *In re Borkowski*) and the fact pattern of the instant rejection are significantly different, and the court decisions are not binding with regard to the instant rejections. For example, in *Gould v. Quigg*,

the claims are drawn to a gas discharge amplifier. The Federal district court accepted the testimony of an expert who relied upon a technical article that was published after the filing date of the application to overcome the prima facie case of lack of enablement. In *Borkowski*, the claims are drawn to a process for producing oxygenated hydrocarbons. The Court of Customs and Patent Appeals indicated that the specification need not contain a working example if one skilled in the art could practice it without undue experimentation and considering the nature of the claimed invention (process for producing hydrocarbons), the few hours of experimentation required were not an undue amount of time. However, neither case cited by Appellant has claims directed to administration of a compound or claims to a pharmaceutical composition.

(b) Predictability

At the bottom of pg 18 through the top of pg 19 of the Brief, Appellant submits that the Examiner has not presented any specific evidence to indicate that the administration of bathocuprione to a subject would have been regarded as unpredictable. Appellant argues that the references cited by the Examiner do not support the enablement rejection. At the top of pg 21 of the Brief, Appellant also asserts that none of the references cited by the Examiner address the issue of whether *in vitro* results with a metal chelator are indicative of *in vivo* results. Appellant argues that no evidence has been presented to support the assertion that the *in vitro* results with bathocuprione are not indicative of the biological results that would be obtained when bathocuprione is administered to a subject. Appellant contends at the bottom of pg 15 of the Brief that there is no logical connection between the statements in Gillmore et al. (Brit J Haematol 99: 245-259, 1997) and the Examiner's position that the effects of bathocuprione

would be unpredictable. Appellant indicates that it is unclear why a person of ordinary skill in the art would not be able to predict the effects of bathcuprione simply because the search continues for a treatment that causes the mobilization of amyloid deposits. At pg 16 and 19 of the Brief, Appellant argues that there is no discussion in Gillmore relating to the use of metal chelators in treating amyloidosis. Appellant states that Gillmore provides no basis for assessing the unpredictability of the effects of a chelator on a subject. Appellant submits that the fact others in the art had not been able to accomplish the results provided by the present invention cannot form the basis for a proper enablement rejection.

Appellant's arguments have been fully considered but are not found to be persuasive. The administration of bathocuprione to a subject for treatment of amyloidosis and to reduce, inhibit, or interfere with Aβ-mediated production of radical oxygen species is unpredictable to the skilled artisan. Specifically, one skilled in the art would not be able to predict that the solubilization of Aβ observed with the brain homogenates would be indicative of results found *in vivo* to treat amyloidosis since brain homogenates are not an art-recognized model for amyloidosis. The skilled artisan would also not be able to predict the effects of bathocuproine or bathocuprione/indomethacin in a subject because the state of the art at the time of filing of the instant application indicated (1) the search was ongoing for a treatment that caused the mobilization of amyloid deposits and (2) the administration of other metal chelators to subjects causes high toxicity and severe physiological side effects (Gillmore et al. Brit J Haematol 99: 245-256, 1997; pg 249, col 2; Fonte et al. J Alzheimer's Disease 3 : 209-219, 2001, Cuajungco et al. Ann NY Acad Sci 290: 292-304, 2000, and Gnjec et al. Frontiers Biosci 7:1016-1023, 2002). Gillmore indicates that few clinical trials have been performed and the approach to treatment of

amyloidosis remains somewhat empirical (pg 250, ¶1). The Examiner acknowledges that Gillmore does not discuss metal chelators in treating amyloidosis. However, Gillmore reviews several types of treatments for amyloidosis that were performed at the time of filing of the instant application and the limitations that have been encountered (pg 250-253). Gillmore teaches that new treatments that inhibit the formation, persistence and effects of amyloid deposits are still required (pg 245, col 2, first full paragraph). Therefore, the state of the prior art establishes the unpredictability of treating amyloidosis *in vivo* since amyloidosis is recalcitrant to treatment. Furthermore, it is noted that a broad, reasonable interpretation of the claims encompasses treatment of such diseases as Alzheimer's disease, which has also proven to be recalcitrant to treatment in the art (see for example, Halliday et al., Clin Exp Pharmacol Physiol 27: 1-8, 2000).

At the top of pg 17 of the Brief, Appellant asserts that Fonte et al., Cuajungco et al., and Gnjec et al. (all cited by the Examiner), do not indicate that the administration of bathocuprione to a subject would have been regarded as unpredictable. Specifically, Appellant argues that Fonte et al. simply indicates that TPEN might be of limited benefit due to its toxicity. Appellant states that the assertion that the benefits of TPEN might be limited does not suggest that TPEN would be ineffective in solubilizing Aβ in the brains of AD patients. Fonte teaches that the extraction of Aβ from the cortex of AD brains was significantly enhanced in a dose dependent manner by the presence of the metal ion chelator, TPEN (Fonte et al., J Alzheimer's Disease 3: 209-219, 2001; see abstract; pg 210, ¶ 2). However, the unpredictable effects of the administration of TPEN are evidenced when Fonte discloses that TPEN is of limited benefit to patients because it is highly toxic (Fonte et al., pg 217, ¶ 1). Fonte also discloses that AβPP transgenic model animals provide a useful means of further evaluating chelators as potential

therapeutic agents for Alzheimer's disease (pg 217, first paragraph). Therefore, Fonte indicates that the *in vitro* results obtained with a metal chelator (such as bathocuprione) require further experimentation and may not be indicative of the results obtained with the metal chelator *in vivo*. The skilled artisan must still resort to trial and error experimentation to determine the optimal route of administration of the metal chelator, as well as the quantity and duration of treatment in a subject to treat amyloidosis. Such trial and error experimentation is considered undue.

Appellant indicates that the document cited in Fonte to support the statement that TPEN is highly toxic (Adler et al., Toxicon 35: 1089-1100, 1997) relates to the administration of TPEN to mice and states that low doses of TPEN were well tolerated. Appellant mentions that Adler et al. is submitted as Exhibit 5. However, this evidence was not timely filed and therefore not considered by the Examiner (37 C.F.R. 1.195 and MPEP § 1207). The final Office Action of 22 May 2003 contained no new grounds of rejection and any new positions or arguments set forth in the Final Office Action were made in response to Appellant's response of 26 February 2003. Therefore, arguments pertaining to the Adler reference are not found persuasive. However, if Adler had been timely submitted, Appellant's arguments still would not have been found persuasive. For instance, Adler teaches the injection of TPEN into mice following challenges with botulinum toxins, not amyloidosis. Furthermore, Adler teaches that higher doses of TPEN (> or = 30 mg/kg), which overlap with the doses disclosed in the instant specification (bottom of pg 48 to the top of pg 49), led to ataxia, loss of coordination, convulsions, and death in 20.3 min or less, as well as cell cytotoxicity (abstract). One skilled in the art would not predict that reducing the dose of a metal chelator (such as TPEN) would avoid toxicity issues while

promoting Aβ resolubilization *in vivo* and treatment of amyloidosis, as asserted by Appellant and required by the claims.

Appellant contends that Cuajungco does not indicate that the administration of metal chelators to subjects is unpredictable (top of pg 18 of the Brief). Appellant argues that Cuajungco supports the conclusion that administration of chelators would not have involved undue experimentation. Appellant states that persons of ordinary skill in the art were able to formulate and administer DFO in an effective manner notwithstanding the technical difficulties associated with this chelator. Appellant submits that surmounting the potential technical difficulties associated with chelators (such as systemic ion depletion and convenient route of administration; see Cuajungco) cannot be regarded as undue experimentation.

Cuajungco teaches that a clinical trial of the chelator, desferrioxamine (DFO), reports that DFO significantly arrested the progression of AD (see pg 299, ¶ 4). However, the unpredictable effects of the administration of DFO is evidenced when Cuajungco discloses that DFO is a charged molecule that does not easily penetrate the blood-brain barrier and is easily degraded after administration (pg 299 ¶ 4). Cuajungco also discloses that the administration of DFO is associated with discouraging difficulties including the nonspecific problems of systemic metal ion depletion (anemia) and the problem of administration of a twice-daily, painful intramuscular injection (pg 299, ¶ 4). The specification of the instant application even teaches that treatment with DFO is impractical because the therapy causes side effects such as anemia due to iron chelation (pg 91, lines 14-16). Appellant does not address Cuajungco's disclosure of the unpredictability of the effects of the administration of metal chelators.

At the second full paragraph at pg 18 of the Brief, Appellant argues that Gnjec provides a general discussion of some of the technical considerations that are associated with chelator therapy. Appellant states that there is no evidence to suggest that such considerations would amount to undue experimentation. Appellant asserts that since chelators have been formulated into pharmaceutical compositions and successfully administered to subjects, addressing the technical considerations set forth in Gnjec can be accomplished using routine methods in the art. However, Gnjec reviews several important points that must be taken into consideration before and during the administration of a metal chelator to a subject, which the instant specification has not addressed with bathocuprione. Specifically, Gnjec discloses the unpredictability of the effects of administration of metal chetators. For example, Gnjec teaches that if the levels of certain metals are decreased excessively below recommended levels, severe physiological side effects may result (under Part IV, important considerations in chelator therapy). Gnjec also indicates that the depletion of metals should be localized to the site of pathology without a systemic depletion of metal ion concentrations. Gnjec discusses that a prerequisite for successful treatment with any chelator will be the requirement for low toxicity and minimum side effects of the drug itself. The unpredictability of the effects of administration of chelators is further evidenced when Gnjec states that "chelators that are not specific for copper (or iron or aluminum) but also bind zinc, may reduce the protective effects of Zn^{2+}, thereby defeating their intended purpose and potentially inducing harmful side effects" (paragraph 2 under Part IV). Gnjec also adds that a successful treatment strategy may involve a combination of several approaches for both the solubilization and inhibition of redox properties of Aβ in AD brain tissue

(last ¶ under part IV). Appellant does not address Gnjec's disclosure of the unpredictability of the effects of administration of metal chelators.

Therefore, taken together, the references cited by the Examiner indicate the unpredictability of the state of the art at the time the invention was made, particularly that *in vitro* Aβ solubilization with a metal chelator are not indicative of the *in vivo* results to treat amyloidosis by reducing, inhibiting or interfering with amyloid beta peptide (Aβ)-mediated production of radical oxygen species, as required by the claims.

(c) In Vitro results

Appellant asserts that the examples in the specification support the conclusion that bathocuprione would be effective at treating amyloidosis when administered to a subject (pg 19, first full ¶, pg 20, 3rd paragraph of the Brief). Appellant argues that there has been no specific evidence presented to contradict the logic underlying this conclusion (pg 20, 3rd-4th paragraph of the Brief). Appellant indicates that the specification demonstrates that bathocuprione promotes the solubilization of Aβ from human brain homogenates. Appellant contends that the physiological conditions that exist in brain homogenates (e.g., pH, ion concentration, macromolecular content, etc.) closely approximate the conditions found in the brain tissue environment *in vivo*. At the bottom of pg 19 of the Brief, Appellant also argues that it was known in the art at the time the application was filed that the regulation of zinc and copper in the brain is abnormal in AD and that these metals are integral components of the Aβ deposits in the brains of AD patients. Appellant adds that zinc- and copper-specific chelators redissolve a significant proportion of Aβ extracted from post-mortem AD affected brain tissue. Contrary to

Appellant's assertions, the *in vitro* results of Aβ solubilization obtained with bathocuprione in the specification of the instant application may not be indicative of the results obtained with bathocuprione *in vivo* to treat amyloidosis. The administration of bathocuprione to a subject may not treat amyloidosis and bathocuprione may not necessarily reduce, inhibit or interfere with amyloid beta peptide (Aβ)-mediated production of radical oxygen species, as required by the claims. The utilization of brain homogenates in Examples 5-7 of the instant specification (pg 90-121) is not an art-recognized, predictive model system for amyloidosis. One skilled in the art would not be able to predict that the results observed with the brain homogenates would be indicative of results found *in vivo* for the treatment of amyloidosis. It is noted that prior to the filing date of the instant application, several transgenic mouse models for amyloidosis and/or Alzheimer's disease had already been developed and were being utilized in laboratories. It is also not clear to the Examiner how brain homogenates approximate brain tissue *in vivo* since there are many other variables present in brain tissue *in vivo* that are not present in the brain homogenates of the specification, such as specific oxygen levels, carbon dioxide levels, temperature, blood/cell circulation, growth factors, other metal ions, etc. Although zinc- and copper-specific chelators redissolve a significant proportion of Aβ extracted from post-mortem AD affected brain tissue (homogenates), these results are not predictive of the treatment of amyloidosis with bathocouprione *in vivo*. The skilled artisan would also not be able to predict that bathocuprione would reduce, inhibit or interfere with amyloid beta peptide (Aβ)-mediated production of radical oxygen species *in vivo,* as required by the claims.

Appellant states at the top of pg 20 of the Brief that a strategy described in the art resulted in slowing progression of AD involved the intramuscular administration of DFO to Alzheimer's

disease patients (Crapper-McLachlan et al., Lancet 337: 1304-1308, 1991). Although Crapper-McLachlan administers DFO intramuscularly to patients, the experiments performed in Crapper-McLachlan are not analogous to the claims of the instant application, which recite the treatment of amyloidosis and wherein the metal chelator reduces, inhibits, or interferes with Aβ peptide-mediated production of radical oxygen species. Crapper-McLachlan only indicates that low doses of DFO slow the clinical progression of the dementia of Alzheimer's disease (abstract, discussion section, first paragraph). Crapper-McLachlan does not disclose that all types of diseases and disorders associated with amyloidosis are treated with DFO or that DFO reduces, inhibits, or interferes with Aβ peptide-mediated production of radical oxygen species, as required by the claims. The specification discloses that "the clinical administration of DFO was reported as being effective in preventing progression of AD; however since DFO chelates Zn^{2+} as well as Fe^{3+} and Al(III), the effect if verifiable, may not have been due to the abolition of the redox activity of Aβ, but may have been due to the disaggregation of Zn^{3+}-mediated Aβ deposits...which may have reduced cortical Aβ burden and, consequently, oxidation stress" (pg 89, lines 1-7). Additionally, although DFO and bathocuprione may both be metal chelators, the positive *in vivo* results of the administration of DFO to a subject for a reduction in the progression of dementia in Alzheimer's disease are not indicative of the results that might occur after the administration of bathocuprione. Bathocuprione has a different chemical make-up and structure than that of DFO, which may cause varied, unpredictable physiological effects after administration to a subject than those of DFO.

Appellant submits at pg 21 of the Brief that the Examiner has the initial burden of showing that the invention is not enabled and cites *Marzocchi,* 439 F.2d at 223, 169 USPQ at

370. Appellant indicates that it is legally improper for the Examiner to require proof that bathocuprione would necessarily treat amyloidosis in a subject when no specific evidence to the contrary has been presented. It is noted that the Examiner has set forth specific evidence and sound scientific reasoning to indicate that the invention encompassed by the claims is not enabled. The Examiner set forth a reasonable explanation of why the scope of protection provided by the claims is not adequately enabled by the specification's description of the invention (pg 4-6 of the Action of 26 August 2002; pg 4-11 of the Action of 22 May 2003). The Examiner had provided a sufficient reason to doubt the statements contained in the specification of the instant application and therefore, a rejection for failure to teach how to make and/or use was proper. Specifically, proper analysis of the Wands factors was provided in the previous Office Actions. Due to the large quantity of experimentation necessary to determine the quantity of bathocuproine or bathocuproine/indomethacin to be administered, the most effective administration route, and the duration of the treatment, the lack of direction/guidance presented in the specification regarding the same, the absence of working examples directed to the same, the complex nature of the invention, and the unpredictability of the effects of the composition *in vivo* (see Fonte et al., Cuajungco et al., Gnjec et al., Gillmore et al.), undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope. Since the PTO met the initial burden of setting forth a reasonable explanation of why the claims are not adequately enabled, the burden shifts to Appellant to provide suitable evidence to indicate that the specification is enabling (see *In re Wright, In re Marzocchi).*

Additionally, the arguments of counsel cannot take the place of evidence in the record. In the instant case, Appellant is asserting that bathocuprione would be effective at treating

amyloidosis when administered to a subject while no data, information, or teaching supports the treatment of amyloidosis by bathocuprione in the instant Specification {see *In re Schulze*, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965); *In re Geisler*, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997) ("An assertion of what seems to follow from common experience is just attorney argument and not the kind of factual evidence that is required to rebut a prima facie case of obviousness.") and MPEP § 716.01(c)}.

(d) Clioquinol

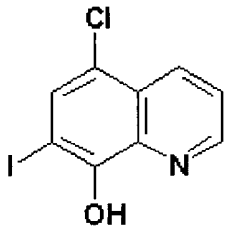
At pg 20 (paragraph 2) and pg 22 of the Brief, Appellant contends that the metal chelator clioquinol has been shown to be effective solubilizing Aβ deposits *in vitro* and in the treatment of Alzheimer's disease and refers to Ritchie et al. (unpublished manuscript; Exhibit 6). Appellant argues that clioquinol, like bathocuprione, was first shown to promote the solubilization of Aβ *in vitro* (Cherny et al., Neuron 30: 665-676, 2001). Appellant adds that the *in vitro* results with clioquinol provided the foundation for subsequent clinical work with this chelator. Appellant states that the clioquinol example shows that a chelator's ability to promote Aβ solubilization *in vitro* likely reflects its ability to treat conditions associated with Aβ deposition *in vivo*. Appellant also contends that the results with clioquinol show that persons of ordinary skill in the art were able to successfully formulate and administer a metal chelator to subjects without undue experimentation. Appellant indicates that since persons of skill in the art were able to successfully formulate and administer clioquinol using only routine methods, there is no reason to believe that persons of ordinary skill could not have also been able to successfully formulate and administer bathocuprione. At the first full paragraph at pg 23 of the Brief,

Appellant argues that the Examiner has not explained why differences in the chemical level between clioquinol and bathocuprione make it unlikely that bathocuprione would exert therapeutic effects when administered to a subject. Appellant asserts that that Examiner has not demonstrated that making and using the claimed invention would have required undue experimentation.

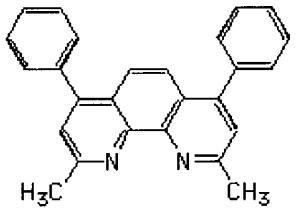
First, Appellant mentions that Ritchie et al. (2003) is submitted as Exhibit 6. This evidence was not timely filed and therefore not considered by the Examiner (37 C.F.R. 1.195 and MPEP § 1207). The final Office Action of 22 May 2003 contained no new grounds of rejection and any new positions or arguments set forth in the Final Office Action were made in response to Appellant's response of 26 February 2003. The new unpublished manuscript has not been peer-reviewed and its contents have not been attested to under 37 CFR 1.132. Therefore, arguments pertaining to the Ritchie unpublished manuscript are not found persuasive. The Ritchie unpublished manuscript does not rise to the level of evidence. The arguments of counsel cannot take the place of evidence in the record. In the instant case, Appellant is asserting that bathocuprione would be effective at treating amyloidosis when administered to a subject while no data, information, or teaching supports the treatment of amyloidosis by bathocuprione in the instant Specification {see *In re Schulze*, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965); *In re Geisler*, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997) ("An assertion of what seems to follow from common experience is just attorney argument and not the kind of factual evidence that is required to rebut a prima facie case of obviousness.") and MPEP § 716.01(c)}.

Additionally, although clioquinol and bathocuprione may both be metal chelators, the positive *in vivo* results of the administration of clioquinol to a subject (a decrease in brain Aβ

deposition and an increase in soluble Aβ; see Cherny et al., Neuron 30: 665-676, 2001) are not indicative of the results that might occur after the administration of bathocuprione. Clioquinol (5-chloro-7-iodo-8-hydroxyquinoline) is specific for copper and zinc ions and has a different chemical make-up and structure than that of bathocuprione (2,9-dimethyl-4,7-diphenyl-1,10-phenanthroline), which is specific for copper.



clioquinol



bathocuprione

Bathocuprione may have different unpredictable physiological effects after administration to a subject than does clioquinol. Furthermore, one skilled in the art cannot predict that all metal chelators will have the same results after administration to a subject. For example, the metal chelators TPEN and DFO, have unpredictable effects after administration to a subject, such as toxicity and difficulty in crossing the blood-brain barrier (see Fonte, Cuajuncgo, and Gnjec). Undue experimentation would still be required of the skilled artisan to determine the proper dosage, duration, and route of administration of bathocuprione because bathocuprione is not chemically/structurally related to clioquinol. The specification of the instant application also does not disclose specific, optimal dosages, duration, and routes of administration of bathocuprione or how to overcome obstacles encountered in prior art disclosures of administration of metal chelators or treating amyloidosis, generally. See Gillmore, Fonte,

Cuajungco, and Gnjec. The specification only discloses numerous modes of administration and a broad range of dosage amounts (pg 48-49). Bathocuprione is a different compound compared to clioquinol and may have varied, unpredictable effects in an individual.

Furthermore, one skilled in the art *at the time the application was filed* would still not have been able to formulate and administer bathocuprione based upon the positive *in vivo* results with clioquinol because the results with clioquinol were published after the filing date of the instant application. The specification and originally filed claims of the instant application do not disclose or recite the administration of clioquinol to a subject. Also, as mentioned above, clioquinol and bathocuprione are not analogous compounds. At the time the application was filed, clioquinol was shown to produce severe side effects in the central nervous system of subject. In particular, patients administered clioquinol developed subacute myelo-optic neuropathy (SMON), a disorder characterized by peripheral neuropathy and blindness. Although the syndrome was mainly confined to Japan and the relationship between clioquinol and SMON was never proven, clioquinol was removed from the worldwide market (Gnjec, Part IV, paragraph 2; Cherny, pg 673, paragraphs 3-4). Gnjec also add that "clioquinol may have additional side effects apart from those related to its own chelating activity for certain metals" (part IV, paragraph 2). Additionally, it is not clear from such references as Cherny et al. that clioquinol treats all possible diseases and disorders characterized by amyloidosis or that clioquinol reduces, inhibits or interferes with amyloid beta peptide (Aβ)-mediated production of radical oxygen species.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

Bridget E. Bunner BEB
Art Unit 1647
March 18, 2004

Conferees
Gary Kunz GAK
Yvonne Eyler

YVONNE EYLER, PH.D
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

GARY KUNZ
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

STERNE KESSLER GOLDSTEIN & FOX
1100 NEW YORK AVENUE NW
SUITE 600
WASHINGTON, DC 20005-3934